Communication

Total Synthesis of Dictyodendrin B

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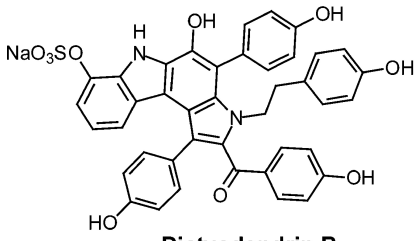
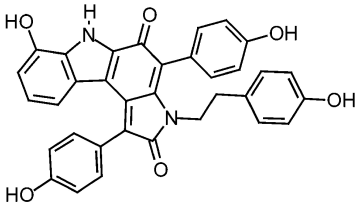


Dictyodendrin B



Dictyodendrin C core

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Total Synthesis of Dictyodendrin B

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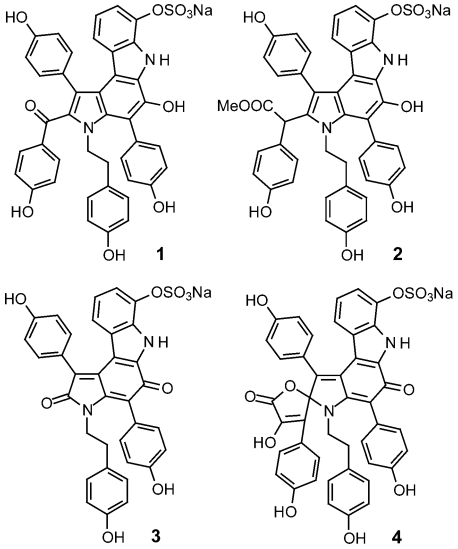
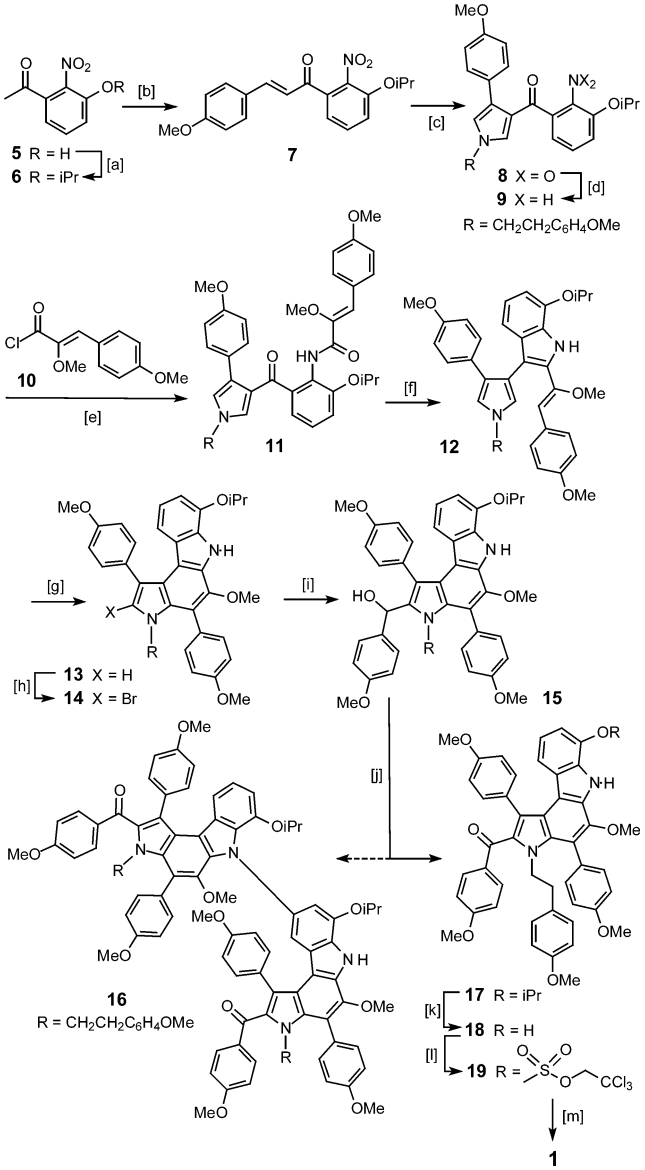
The finite lifespan of somatic cells results from the shortening of single-stranded "telomeric" DNA protecting the ends of the chromosomes. These telomeres are progressively shortened with successive rounds of replication until they reach a critical length at which apoptosis is triggered to prevent further aging. Tumor cells, however, are able to maintain their telomeric ends by the action of telomerase. This enzyme has reverse-transcriptase properties and is overexpressed in >85% of all malignant cells but is virtually absent in normal tissue[1] and, therefore, constitutes a particularly promising molecular target in the quest for more selective chemotherapeutic agents for the fight against cancer.[2]



Since the number of telomerase inhibitors from natural sources is fairly limited,[2,3] a recent publication disclosing the structure and activity of the dictyodendrins is particularly noteworthy.[4] These very scarce alkaloids isolated from the marine sponge *Dictyodendrilla verongiformis* effect 100% telomerase inhibition at a concentration of 50 μg/mL, although no further biochemical profiling was reported. Dictyodendrins, such as **1**−**3**, are close relatives of the spirocyclic aldose reductase inhibitor **4**[5] and constitute the first naturally occurring pyrrolo[2,3-*c*]carbazole derivatives known in the literature. With the hope to contribute to the biological assessment of these structurally unique compounds,[6] we launched a program aiming at the development of a concise, flexible, and potentially scalable entry into this class of marine alkaloids. The total synthesis of dictyodendrin B (**1**) outlined below represents the first step along these lines.

Acetophenone **5** served as appropriate starting material,[7] which was protected as isopropyl ether **6** prior to condensation with *p*-$MeOC_6H_4CHO$ (Scheme 1). The resulting chalcone **7** was exposed to toluenesulfonylmethyl isocyanide (TosMIC) and NaH at low temperature[8] to afford pyrrole **8** after in situ N-alkylation with *p*-$MeOC_6H_4(CH_2)_2Br$. Subsequent reduction of the nitro group

Scheme 1 [a]



[a] Conditions: (a) 2-bromopropane, K_2CO_3, DMF, 100 °C, 99%; (b) *p*-$MeOC_6H_4CHO$, NaOMe, MeOH, 70 °C, 74%; (c) (i) TosMIC, NaH, THF, −30 °C; (ii) *p*-$MeOC_6H_4(CH_2)_2Br$, reflux, 83%; (d) Fe powder, aq. HCl, EtOH, 96%; (e) **10**, CH_2Cl_2, Et_3N, DMAP cat., 89%; (f) $TiCl_3$/2 KC_8, DME, pyridine, reflux, 71−93%; (g) *hν*, MeCN, Pd/C cat., $C_6H_5NO_2$, 81%; (h) NBS, THF, 0 °C, 69%; (i) (i) MeLi, THF, −78 °C; (ii) *n*-BuLi, −78 °C; (iii) *p*-$MeOC_6H_4CHO$, −78 °C → rt, 97%; (j) TPAP (10%), NMO, MS 4 Å, CH_2Cl_2 (0.01 M), 66% (**17**), 16% (**16**); (k) BCl_3, CH_2Cl_2, −20 °C, 85%; (l) $Cl_3CCH_2OSO_2Cl$, DABCO, CH_2Cl_2, 92%; (m) (i) BCl_3, TBAI, CH_2Cl_2, 0 °C → rt; (ii) Zn, $HCOONH_4$, MeOH, 58%.

with Fe/HCl provided aniline **9** in excellent yield on a multigram scale, which was condensed with acid chloride **10**[9] under standard

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conditions to give amide **11** as the key compound of the envisaged synthesis route.

Previous investigations from this laboratory had shown that ketoamides, on treatment with low-valent titanium, convert to indole derivatives even in the presence of other reducible sites.[10−12] Application of this protocol to substrate **11** afforded the desired product **12** in up to 93% isolated yield on exposure to titanium−graphite (prepared from $TiCl_3$ and 2 KC_8)[13] in refluxing DME. Thereby, it turned out beneficial to buffer the slightly Lewis acidic reaction medium with pyridine to prevent partial cleavage of the labile enol ether moiety in the substrate. Indole **12** thus formed is set up for subsequent closure of the dictyodendrin core by a 6π-electrocyclization.[14] This transformation proceeded smoothly upon irradiation of **12** with UV light (Hanovia Hg lamp, 250 W) in MeCN; addition of Pd/C and nitrobenzene[15] to the reaction medium causes concomitant aromatization of the product initially formed, thus giving rise to the desired pyrrolocarbazole **13** in 81% yield in a single operation.

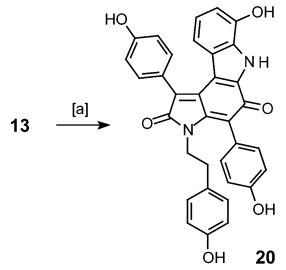
Initially, a Friedel−Crafts acylation of the activated 2-position of **13** was envisaged to complete the carbon skeleton of **1**.[16] In the presence of Lewis acids, however, this compound is subject to a complex skeletal rearrangement rather than acylation, thus forcing us to pursue a different route. Gratifyingly, treatment of **13** with NBS resulted in a selective bromination to give the somewhat unstable product **14**, which was subjected to metal−halogen exchange with *n*-BuLi (after deprotonation of the −NH group with MeLi). The resulting aryllithium species could be quenched with *p*-$MeOC_6H_4CHO$ to afford product **15** in excellent yield.[17]

The subsequent oxidation of the benzylic alcohol moiety in **15** under various conditions turned out rather capricious and afforded variable amounts of a byproduct **16** in addition to the expected ketone **17**. Extensive NMR investigations were necessary to unravel the constitution of **16** as an unsymmetrical dimer, in which the two subunits are connected via C8 and the carbazole N-atom, respectively.[18] The dimeric nature of **16**, however, suggested that the oxidation might respond to the dilution of the reaction mixture. In fact, the yield of the desired ketone **17** could be increased to 66% when the oxidation was performed in dilute (0.01 M) CH_2Cl_2 solution with tetra-*n*-propylammonium perruthenate (TPAP, 10 mol %) and NMO.[19] Selective cleavage of the isopropyl ether in **17** with BCl_3 followed by reaction of the resulting phenol **18** with trichloroethyl chlorosulfuric acid ester [20] gave aryl sulfate **19** in excellent yield. This compound allowed for exhaustive demethylation with BCl_3/(n-Bu)$_4$NI[21] without affecting the labile sulfate group. Reductive cleavage of the chloroethyl ester with Zn/HCO_2-NH_4 proceeded smoothly and completed the first total synthesis of dictyodendrin B (**1**), the spectroscopic data of which matched those reported in the literature.[4]

The chosen route is not only highly productive (13 steps in the longest linear sequence, 8% yield overall) but also should allow for substantial structural variations. As a first step along these lines, we checked whether compound **13** could be channeled toward dictyodendrin C (**3**) featuring an extended quinoid motif in its core. Gratifyingly, global deprotection of **13** with BBr_3 was accompanied by a spontaneous and selective oxidation with formation of quinone **20** (Scheme 2). Notably, this compound does not only represent desulfated dictyodendrin C but also constitutes the common "degradation" product to which *all* naturally occurring dictyodendrins converge upon hydrolysis.[4]

Further studies on the synthesis and biological evaluation of this intriguing class of natural products are underway and will be reported in due course.

Scheme 2 [a]



[a] Conditions: (a) BBr_3, cyclohexene, CH_2Cl_2, −78 °C → rt, 49%, cf. text

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Supporting Information Available: Full experimental details and copies of spectra of relevant intermediates. This material is available free of charge via the Internet at http.//pubs.acs.org.

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